

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
 BOWDERY, A., O.
 D/IPR
 FORMALITIES SECTION (DERA)
 Poplar 2, MOD Abbey Wood #19
 Bristol BS34 8JH
 UNITED KINGDOM

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INVITATION TO PAY ADDITIONAL FEES
(PCT Article 17(3)(a) and Rule 40.1)

MSD - DPA

Applicant's or agent's file reference IPD/P1206/WOD	PAYMENT DUE Date of mailing <small>(day/month/year)</small> 20/03/2000
International application No. PCT/GB 99/03538	International filing date <small>(day/month/year)</small> 26/10/1999
Applicant THE SECRETARY OF STATE FOR DEFENCE et al.	

1. This International Searching Authority

(i) considers that there are 36 (number of) inventions claimed in the international application covered by the claims indicated ~~XXXX~~ on the extra sheet:

and it considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated ~~XXXX~~ on the extra sheet:

(ii) has carried out a partial international search (see Annex) will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.:

1-5, 7, 8, 21-30 (all partially)

(iii) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid

2. The applicant is hereby **invited**, within the time limit indicated above, to pay the amount indicated below:

GBP 638, - x 35 = GBP 22 330, -
Fee per additional invention number of additional inventions total amount of additional fees

Or, EUR 945, - x 35 = EUR 33 075, -

The applicant is informed that, according to Rule 40.2(c), **the payment of any additional fee may be made under protest**, i.e., a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive.

3. Claim(s) Nos. _____ have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the International Searching Authority

 European Patent Office, P.B. 5818 Patentlaan 2
 NL-2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer
 Véronique Baillou

EINSCHEIBEN

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-5,7,8,21-30 (all partially)

A protein having luciferase activity and at least 60% similarity to the luciferase from *Photinus pyralis* wherein in the sequence of the enzyme the amino acid residue at position 214 is different to the amino acid which appears in the corresponding wild-type sequence and wherein the luciferase enzyme has increased thermostability as compared to an enzyme having the amino acid of the wild-type luciferase at this position. Kit comprising the protein, nucleic acid encoding the protein, cell transformed with said vector and plant comprising such cells. Method for producing the protein comprising culturing such cell or growing such plant. Use of the protein in a bioluminescent assay.

~~2-36~~ Claims: 1-30 (all partially)

Subjects 2 to 36:

Each of the eight remaining substitution mutants (at positions 232, 295, 14, 35, 105, 234, 420 and 310) of *Photinus pyralis*; each of the nine substitution mutants (at positions 216, 234, 297, 16, 37, 106, 236, 422 and 312) of *Luciola mingrellica*; each of the nine substitution mutants (at positions 216, 234, 297, 17, 38, 107, 236, 422 and 312) of *Luciola cruciata*; each of the nine substitution mutants (at positions 216, 234, 297, 17, 38, 107, 236, 422 and 312) of *Luciola lateralis* which are recited in the claims.

The claims are considered to lack unity of invention since they are directed to thirty-six (36) separate inventions not so linked as to be based on a common underlying inventive concept. According to Rule 13.3 PCT, the determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim. As acknowledged by the Applicant on page 2 of the description, substitution mutants of luciferase from *Photinus pyralis*, *Luciola mingrellica*, *Luciola cruciata* and *Luciola lateralis* having increased thermostability as compared with the wild-type luciferase from which they derive were known in the art at the claimed priority date (see EP-A-524 448 and WO-A-95/25798). In the light of the above documents cited by the applicant, the problem underlying the present application is to be seen in the provision of further substitution luciferase mutants of *Photinus pyralis* or *Luciola* having such increased thermostability. As a solution to the above problem, the applicant now proposes in claim 1 different alternative solutions represented by mutants of luciferase having wild-type amino acids residues at certain positions replaced by another amino acid. Although all the proposed alternative solutions derive from the

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analogous application of the same known amino acid substitution strategy known from the documents identified by the Applicant, this per se cannot constitute an unitary link among them. In fact, in the light of the disclosure in said documents of a generally applicable applicable strategy of converting an amino acid residue at a specific position into an another, preferably hydrophobic, amino acid residue and its exemplification in respect of the luciferases from Photinus pyralis and Luciola luciferases, each successive identification of further mutant luciferases produced following this strategy constitutes a separate, independent invention. Also the common utility (use in a bioluminescent assay) cannot provide such a unitary link because this was the known purpose of the prior art strategy and means as well. For the foregoing reasons, there is no "special technical feature" in the sense of Rule 13.2 PCT to link the mentioned groups 1 to 36 of inventions.

Annex to Form PCT/ISA/206
COMMUNICATION RELATING TO THE RESULTS
OF THE PARTIAL INTERNATIONAL SEARCH

International Application No

PCT/GB 99/03538

1. The present communication is an Annex to the invitation to pay additional fees (Form PCT/ISA/206). It shows the results of the international search established on the parts of the international application which relate to the invention first mentioned in claims Nos.:
1-5, 7, 8, 21-30
2. This communication is not the international search report which will be established according to Article 18 and Rule 43.
3. If the applicant does not pay any additional search fees, the information appearing in this communication will be considered as the result of the international search and will be included as such in the international search report.
4. If the applicant pays additional fees, the international search report will contain both the information appearing in this communication and the results of the international search on other parts of the international application for which such fees will have been paid.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 46729 A (MURRAY JAMES AUGUSTUS HENRY ;SECR DEFENCE (GB); LOWE CHRISTOPHER R) 22 October 1998 (1998-10-22) the whole document ---	1-5, 7, 8, 21-30
A	EP 0 524 448 A (KIKKOMAN CORP) 27 January 1993 (1993-01-27) cited in the application the whole document ---	1-5, 7, 8, 21-30
A	WO 95 25798 A (SECR DEFENCE BRIT ;LOWE CHRISTOPHER ROBIN (GB); WHITE PETER JOHN () 28 September 1995 (1995-09-28) cited in the application the whole document -----	1-5, 7, 8, 21-30



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Patent Family Annex

Information on patent family members

International Application No

PCT/GB 99/03538

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9846729	A 22-10-1998	AU 6929398 A EP 0973874 A		11-11-1998 26-01-2000
EP 0524448	A 27-01-1993	DE 69229376 D US 5229285 A JP 5244942 A		15-07-1999 20-07-1993 24-09-1993
WO 9525798	A 28-09-1995	AU 697883 B AU 1954595 A BR 9507140 A CA 2186144 A CN 1149318 A EP 0751996 A FI 963741 A GB 2301592 A,B JP 9510610 T NO 963983 A		22-10-1998 09-10-1995 30-09-1997 28-09-1995 07-05-1997 08-01-1997 20-11-1996 11-12-1996 28-10-1997 23-09-1996